Deproteinized Bovine Bone Mineral Enriched with Hyaluronate A comparative Clinical ,Biochemical and Radiographic study

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Abstract

Aim: the aim was to compare the clinical, biochemical and radiographic effectiveness of Cerabone versus Cerabone Plus in Stage III periodontitis patients. **Patients and methods:** patients with periodontitis were enrolled and randomly assigned into two groups: Group 1 (Cerabone®): treated with deproteinized bovine bone mineral (DBBM). Group 2 (Cerabone® Plus): treated with DBBM enriched with hyaluronate (Cerabone Plus®). Clinical evaluation including Plaque index [(1)] ,Gingival index , Probing Depth (2), and Clinical Attachment Loss (CAL) were recorded at baseline,6,9,12 month, while biochemical evaluation includingbone morphogenetic protein (BMP-2). Radiographic defect fill, and Bone density assessed. **Results**: Probing Depth and Clinical Attachment Loss (CAL) demonstrated statistically significant reductions compared to baseline in both groups. Cerabone Plus group consistently showed slightly higher mean of CAL and PD reduction compared to the Cerabone group. Regarding biochemical markers, Cerabone plus Group demonstrated significantly higher BMP-2 concentrations compared to Cerabone Group ($p < 0.05$). The Cerabone Plus group exhibited slightly higher and more rapid radiographic bone gain compared to Cerabone alone. **Conclusions**: Cerabone Plus (HA-enriched bovine xenograft) appeared to be slightly superior than Cerabone alone in the treatment of intrabony defects in Stage III periodontitis.

Keywords: Bone Regeneration, Intrabony Periodontal Defects, Cerabone Plus ,BMP-2

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Introduction

Periodontitis is highly prevalent worldwide, representing one of the most common chronic diseases of humankind [(1)]. Epidemiological studies have reported that nearly half of the adult population suffers from some form of periodontitis, with severe cases affecting 10–15% of adults globally [(2)]. The prevalence increases with age, with elderly individuals being at higher risk due to cumulative tissue destruction and systemic health conditions. Socioeconomic factors, smoking, poor oral hygiene, and systemic diseases such as diabetes are significant contributors to disease prevalence and severity. Understanding the epidemiology of periodontitis is essential to highlight its public health burden and to justify the need for preventive and therapeutic strategies [(3)].Periodontal regeneration defined as the reconstitution of the lost periodontal apparatus, including new cementum, periodontal ligament, and alveolar bone. Unlike repair, which leads to the formation of long junctional epithelium, true regeneration aims to restore the original architecture and function of periodontal tissues. Advances in regenerative techniques, including guided tissue regeneration, application of growth factors, and use of biomaterials, have greatly enhanced the potential for periodontal regeneration. These approaches are particularly valuable in treating intrabony defects, furcation involvement, and peri-implant bone loss[(4)] . Recent advances in biomarker research have enabled the evaluation of periodontal disease activity and healing potential through the analysis of gingival crevicular fluid (GCF)[(5)]. Biomarkers such as Bone Morphogenetic Protein-2 (BMP2) are crucial indicators of bone metabolism and periodontal regeneration. BMP2 is a key growth factor that promotes osteogenesis(6).

Bone grafting bio-materials play a central role in regenerative periodontal therapy. Among them, deproteinized bovine bone mineral (DBBM), commercially available as Cerabone, has been widely used as a xenograft due to its osteoconductive properties, biocompatibility, and slow resorption rate [(7)] . Cerabone Plus, a modified form of Cerabone, incorporates hyaluronic acid to enhance cell

adhesion, migration, and differentiation, thereby potentially improving regenerative outcomes. These biomaterials provide a scaffold for new bone formation space maintainers, facilitating periodontal and peri-implant regeneration [8] This study was undertaken to check, clinically, biochemically and radiographically, the efficacy of xenograft with hyaluronic acid in the treatment of Stage III periodontitis patients with intrabony defects.

Patients and methods

Study design: A randomized controlled clinical,biochemical and radiographic trail

Study setting and population

A randomized controlled clinical, biochemical and radiographic, trail carried out on twenty patients of both sexes attending at the outpatient clinic, Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University (Assiut branch).

Ethical Approval

All eligible patients were thoroughly informed to the nature, potential risks and benefits of their participation in the study and signed their informed consent documents. The study protocol was approved by the ethical committee, Faculty of Dental Medicine, Al-Azhar University, Assiut branch. (Number: AUARE C202300001-03)**.**

Eligibility criteria

Inclusion and exclusion criteria

1. All patients were selected free from any systemic disease according to the criteria of Cornell medical index[9].
2. Female patients were neither pregnant nor taking contraceptive pills.
3. All patients should have good compliance, acceptable for oral hygiene instructions, non-smoker and cooperative.
4. No previous history of periodontal surgery in the diseased region in the last 6 months or taking antibiotics or anti-inflammatory in the last 3 months.
5. All sites with teeth of endodontic lesion or inadequate endodontic treatment and gingival recession were excluded from the study.

Patients grouping

Patients were divided randomly into two groups: **Group I:** 10 periodontitis patients' stage III with intrabony defects received open flap department combined with Cerabone, **Group II**: 10 periodontitis patients' stage III with intrabony defects received open flap surgery combined with Cerabone plus

Intervention

Intervention

Following completion of initial phase of periodontal therapy. Full-thickness mucoperiosteal flaps were performed starting on tooth distal to the tooth being treated with minimum extension of one tooth more than treated area. Thorough debridement and root planning of the exposed root surfaces was performed by hand instrumentation and air scaler. In **group I** patients, bone graft substitute (Cerabone) was prepared by mixing with few drops of normal saline and applied to the defect and condensed with spherical plugger then covered with collagen membrane **Fig [1]**. In **group II** patients, bone graft substitute (Cerabone plus) was prepared by mixing with few drops of normal saline and applied to the defect and condensed with spherical plugger then covered with collagen membrane **Fig [2]**.

Clinical evaluation

All patients were evaluated clinically at; **baseline, 3-, 6-, 9- and 12-months** post surgically using the following periodontal parameters:

Plaque index (PI)[10]

Gingival index (GI)[10]

Probing pocket depth (PPD)[11]**;** was recorded by William 's graduated periodontal probe.

Clinical attachment level (CAL)[11]**;** was measured using William 's graduated periodontal probe.

Biochemical Analysis

The concentrations of bone morphogenetic protein-2 (BMP-2) in GCF were quantified using enzyme-linked immunosorbent assay (ELISA) at baseline ,1week, 4weeks ,12 weeks.

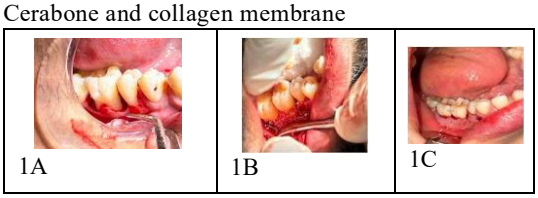
Radiographic evaluation

Radiographic evaluation of the marginal bone level and bone density **Fig [2,4]** of the surgical defects were done at; baseline, 6, and 12months post surgically ,the study using:

1- Cone beam CT radiographs (CBCT).

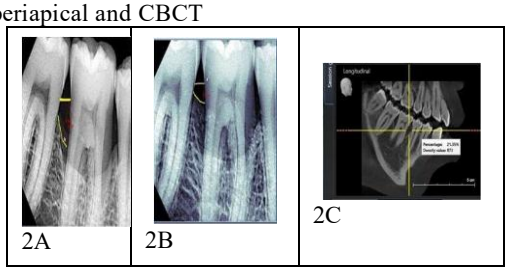
2- Standardized periapical radiographs.

Figure [1];Group 1: Open flap debridement with Cerabone and collagen membrane



(1A)flab reflection showing Intrabony defect, **(1B)** Cerabone graft application, **(1C)** suturing

Figure [2];Group 1: radiographic evaluation periapical and CBCT



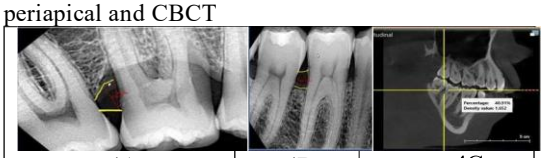
(2A) Preoperative periapical radiograph showing intrabony pocket, **(2B)** periapical radiograph after 12months**,(2C)** Radiographic CBCT showing bone density after 12 months

Figure [3];Group 2: Open flap debridement with Cerabone plus and collagen membrane


3A 3B 3C

(3A)flab reflection showing Intrabony defect, **(3B)** Cerabone graft application, **(3C)** Cerabone graft covered with collagen membrane

Figure [4];Group 2: radiographic evaluation periapical and CBCT


4A 4B 4C

(4A) Preoperative periapical radiograph showing intrabony pocket, **(4B)** periapical radiograph after 12months, **(4C)** Radiographic CBCT showing bone density after 12 months

Statistical analysis

The data were collected, tabulated, computed and analyzed using using Kolmogorov- Smirnov and Shapiro-Wilk tests

Results

Pocket Depth

Table (1): Comparison of (Clinical parameters) Pocket depth **(PD)** and Clinical Attachment Loss **(CAL)** for the 2 groups at different time intervals

Time Interval	Group 1	Group 2	t-test	p-value	Sig
Baseline (PD)	6.13 (3.96)	5.60 (4.79)	0.332	0.742	NS
Baseline (CAL)	6.383 (3.206)	5.827 (4.578)	0.386	0.703	NS
3 months (PD)	5.73 (4.04)	3.40 (1.12)	2.154	0.040	*
3months (CAL)	6.213 (3.468)	3.880 (2.594)	2.087	0.046	*
6 months (PD)	2.27 (1.34)	3.27 (0.88)	2.420	0.022	*
6months (CAL)	5.947 (3.395)	3.707 (2.412)	2.083	0.046	*
9 months (PD)	2.80 (2.62)	3.23 (0.78)	0.613	0.545	NS
9months (CAL)	3.467 (2.850)	2.880 (0.883)	0.761	0.453	NS
12 months (PD)	2.47 (1.13)	3.20 (0.86)	2.001	0.061	NS
12months (CAL)	2.540 (0.980)	1.987 (0.409)	2.011	0.063	NS
P (PD)	0.000 \	0.02*			
P (CAL)	.001	.003			

t: independent t-test

The significance level was set at $P \leq 0.05$.

t: independent t-test

The significance level was set at $P \leq 0.05$.

Bone Morphogenetic Protein:

Table (2): Comparison of BMP2 (pg/ml) Concentrations Between the Two Groups at Different Time Intervals

Time Interval	Group 1 Mean (SD)	Group 2 Mean (SD)	t-test	p-value	Sig
Baseline	48.63 (43.18)	69.42 (41.95)	1.337	0.192	NS
1 week	111.52 (125.10)	348.62 (177.33)	4.232	0.000	**
4 weeks	185.30 (244.40)	1739.66 (2909.97)	2.061	0.049	*
12 weeks	205.84 (112.75)	1979.01 (2081.77)	3.294	0.003	**
p-value	0.022*	0.008**			

t: Independent samples t-test

NS: Non-significant

Significant at $P < 0.05$

Highly significant at $P < 0.01$

Marginal Bone Level (Periapical Radiographs)

Table (3): Comparison of Periapical radiographic marginal bone level and Cone Beam CT (CBCT) radiographic bone density for the two groups :

Time intervals	Group 1	Group 2	t-test	P-value	Significance
Baseline (periapical)	7.253 (1.662)	6.640 (1.538)	1.049	0.303	NS
Baseline (CBCT)	896.267 (45.091)	1010.067 (220.474)	1.959	0.060	NS
6 months	4.600 (1.352)	3.254 (2.140)	2.059*	0.049	S

(periapical)					
6 months (CBCT)	1046.067 (89.541)	1115.400 (94.561)	2.062*	0.049	S
12 months (periapical)	2.680 (0.547)	2.147 (1.252)	1.512	0.142	NS
12 months (CBCT)	1117.267 (57.021)	1213.933 (52.553)	4.828**	0.000	S
P	.000	.000			
P	0.000	.001			

t: independent t-test
The significance level was set at $P \leq 0.05$.

DISCUSSION

Periodontitis characterized by non-reversible tissue destruction resulting in progressive attachment loss, which in turn may leads to tooth loss. It is established that the sixth most prevalent disease of mankind is severe periodontitis [(12)]. Occasionally, overgrowth or new properties are introduced by a subset of bacterial species that contribute to periodontal destruction. Periodontitis results in osseous defects of different morphological forms and three types of defects are caused by site-specific periodontal breakdown that is suprabony (horizontal) defects, intra-bony (vertical) defects and inter-radicular (furcation) defects, vertical defects are more suitable for regenerative processes [(13)]. This study aimed to evaluate the clinical biochemical and radiographic outcomes of using Cerabone versus Cerabone Plus in Stage III periodontitis patients.

The present study used a combination between xenograft and hyaluronic acid (Cerabone plus) in attempt to accelerate new bone formation and increase bone volume in intrabony defects, this is in agreement of De Oliveira et al.[(14)] . found that HA combined with xenografts significantly improved early osteoid deposition, suggesting enhanced early osteogenesis, even though long-term trabecular organization was comparable to xenografts alone. Additionally, this study collectively supports the radiographic outcomes observed in the present investigation and emphasize the biological advantage of HA-enriched xenografts in promoting earlier and more robust bone regeneration. Moreover, the use of Cerabone®, a bovine-derived xenograft, has been extensively documented as a highly biocompatible osteoconductive material with stable volume and long-term graft integration, especially in periodontal and peri-implant bone defects. This confirmed by a study [(15)] found that Decortication plus Cerabone™ significantly improved the clinical and radiographic parameters of intrabony defects at 9 months after treatment when compared to Decortication plus DFDBA. RVG and CBCT analysis were shown to be similar in the analysis of intrabony defect depth reduction and defect resolution.

The inclusion of hyaluronic acid (Cerabone Plus) in the test group is supported by Kyyak et al. [(16)] who found that HA-functionalized xenografts significantly enhance osteoblast proliferation, migration, and attachment, contributing to improved regenerative microenvironments. These considerations reinforce the scientific rationale for the study design, patient demographics, and material selection used in this investigation. In contrast, Kaya et al. [(17)] reported no statistically significant differences in bone or attachment gain between standard xenografts and those enhanced with hyaluronic acid [(18)]. Additionally, Lorenzi et al. [(19)] demonstrates inconsistent evidence for HA's added value in bone regeneration across clinical settings Despite these variations, the present findings suggest that Cerabone Plus contributes to accelerated periodontal healing, particularly during critical early and mid-term intervals, even though the overall regenerative outcomes at 12 months were comparable between the groups, aside from the noted differences in timing and speed of healing.

A significant reduction in probing pocket depth (PPD) and bleeding index (BI), along with gains in clinical attachment loss (CAL), were observed in both groups at 3, 6, and 12 months. However, the Cerabone Plus group showed slightly in PD reduction and CAL gain compared to Cerabone alone, particularly at 3 and 6 months. This may be attributed to the added hyaluronic acid, which promotes early soft tissue healing and enhances the regenerative environment, This findings align with those of Brignardello[(20)], who reported that HA-enriched grafts result in superior soft tissue outcomes and increased stability of the periodontal architecture In comparison, our study demonstrates that the adjunctive use of hyaluronic acid– enriched xenograft (Cerabone Plus) yields clinically and biologically significant improvements in bone regeneration. Also, this is supported by previous findings from Eliezer et al. [(21)], who observed enhanced periodontal healing and improved radiographic bone fill when hyaluronic acid was used in conjunction with bone substitutes in intrabony defects.

Similarly, more recent systematic review[(22)] concluded that HA, when used with regenerative procedures, resulted in superior CAL gain and bone formation outcomes compared to controls. In contrast, earlier research's [(23, 24)] has shown that while open-flap debridement alone can improve probing depth and clinical attachment levels, the degree of new bone formation remains limited in the absence of grafting materials.

In the present study, the follow-up intervals for assessing biochemical markers specifically bone morphogenetic protein-2 (BMP-2) were strategically chosen at 1, 4, and 12 weeks to capture distinct phases of periodontal wound healing and bone regeneration. The 1-week interval reflects the early inflammatory and healing response, during which transient alteration in pro- and anti-inflammatory biomarkers such as BMP-2 are expected. At this stage, BMP-2 levels typically peak to initiate osteogenic signaling. The 4-week time point corresponds to the early proliferative and matrix deposition phase, when expression begins to rise, signaling active mineralization. Finally, the 12-week mark allows for assessment during the early remodeling phase, providing insights into sustained biomarker activity and long term osteogenic outcomes.

BMP-2 levels in the gingival crevicular fluid (GCF) increased progressively post-surgery, with significantly higher concentrations in the Cerabone Plus group at 4 and 12 weeks. The mean BMP-2 at 12 weeks in Cerabone Plus was approximately 1974 pg/ml versus 164.6 pg/ml in the Cerabone group ($p < 0.001$). BMP-2 is a critical osteoinductive factor, and its elevation indicates enhanced bone regeneration.This result is consistent with the findings of Jungju Kim et al. [25]who demonstrated that HA-based scaffolds facilitate BMP-2 expression and subsequent osteoblastic differentiation . Similar outcomes were reported by a recent study[26] who showed that combining HA with BMP-2 enhanced bone repair in critical-sized defects. Current evidence does not report any decrease in BMP-2 levels following periodontal regeneration with hyaluronic-acid–enriched xenografts. To the contrary, most studies document maintained or elevated BMP-2 expression, which supports the regenerative effect of HA in osteogenesis .

Periodontal regeneration is a dynamic process involving bone formation and remodeling, during which osteoblasts are activated to produce, a key non collagenous protein and recognized marker of bone maturation and mineralization.

Periapical radiographs showed faster bone fill in the Cerabone Plus group at 6 and 12 months. Moreover, CBCT analysis revealed significantly higher bone density values in the Cerabone Plus group at both 6 and 12 months, indicating superior quality and volume of regenerated bone. These outcomes supported by findings of Wanget al. [27], who demonstrated that graft materials combined with HA or other biologically active agents yield more consistent and radiographically evident bone regeneration. Additionally, have shown that HA enhances vascularization a prerequisite for stable and dense bone formation.

The present study demonstrated that Cerabone Plus significantly enhanced both radiographic bone level and CBCT-measured bone density compared to Cerabone alone, some studies have produced contrasting outcomes. For example, Lorenzi et al. [19] conducted a systematic review and meta-analysis on the regenerative effects of hyaluronic acid in bone augmentation and found that although HA may support soft tissue healing, it did not significantly improve new bone formation or bone volume gain when combined with graft materials ($p > 0.05$).

Sundar et al. [28] observed that while HA improved early wound healing parameters, it did not lead to a significant difference in bone density as assessed by radiographic gray scale values at 6 months postoperatively. These findings suggest that the osteogenic benefits of HA may be protocol-dependent, and its efficacy could vary based on defect morphology, carrier material, or patient-related factors. Thus, while our results support the utility of Cerabone Plus in enhancing bone regeneration. So, studies are warranted to determine the conditions under which HA consistently improves bone-related outcomes.

Finally, Cerabone plus, a combination of xenograft with HA is provided dry and has to be hydrated before use. Upon hydration with saline or blood, it forms a malleable putty bone grafting material, which facilitate application and adaptation and reduces partial distribution in the defect. In addition, the implementation of HA in combination with bone substitute materials may be promising to overcome any limitation in the soft and hard tissue regeneration.

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